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# There Is No Way to Avoid Systematic Prostate Biopsies in Addition to Multiparametric Magnetic Resonance Imaging Targeted Biopsies

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**Article info**

***Article history:***
Accepted March 6, 2019

**Associate Editor:**
Gianluca Giannarini

***Keywords:***
Targeted biopsy
Random biopsy
Fusion biopsy
Clinically significant prostate cancer outside the index lesion
Multiparametric magnetic resonance imaging

**Abstract**

***Background:*** Whether or not adding systematic biopsies (transrectal ultrasound-guided biopsy [TRUS-Bx]) to targeted cores in patients with a lesion detected at multiparametric magnetic resonance imaging (mpMRI) is still a debated topic.

***Objective:*** To identify patients who can avoid TRUS-Bx at the time of mpMRI targeted biopsy (MRI-TBx) relying on individual patient probability to harbour clinically significant prostate cancer (csPCa) outside the index lesion (IL).

***Design, setting, and participants:*** A total of 339 European and 441 North American patients underwent fusion MRI-TBx and concomitant TRUS-Bx at two tertiary care referral centres between 2013 and 2017.

***Outcome measurements and statistical analysis:*** The study outcome was csPCa, defined as a Gleason score at biopsy of $\geq$7, outside the IL. Multivariable logistic regression analyses (MVAs) were performed to develop a predictive model for the study outcome. Multivariable-derived coefficients were used to develop a novel risk calculator in each cohort. The models were evaluated using the area under the curve (AUC), calibration plot, and decision-curve analyses.

***Results and limitations:*** In the European cohort, csPCa detection rate was 55%. The csPCa detection rate for TRUS-Bx was 41%. At MVAs, prostate volume, previous negative biopsy, and Prostate Imaging Reporting and Data System versions 4 and 5 were independent predictors for the presence of csPCa outside the IL. The multivariable model had an AUC of 0.78. Omitting TRUS-Bx in patients with a calculated risk of <15% would have spared 16% of TRUS-Bx at the cost of missing 7% of csPCa. Similar findings were obtained when the same analyses were performed in the North American cohort. No net benefit was observed for low-threshold probabilities (<15%) of the each model relative to the standard of care (performing TRUS-Bx in addition to MRI-TBx to all patients) in both cohorts. The study is limited by its retrospective design.

***Conclusions:*** We failed to identify those patients who might safely benefit from MRI-TBx alone. The combination of MRI-TBx and TRUS-Bx should strongly be considered the best available approach.

***Patient summary:*** In the presence of positive multiparametric magnetic resonance imaging (mpMRI) of the prostate, physicians should always perform systematic sampling of the prostate in addition to mpMRI targeted biopsy.



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https://doi.org/10.1016/j.euo.2019.03.002
2588-9311/

## 1. Introduction

The diagnosis of prostate cancer (PCa) as per current urological guidelines relies on the serum prostate-specific antigen (PSA) levels and digital rectal examination (DRE) [1,2]. An elevated PSA level and/or a positive DRE trigger a systematic 10–12-core transrectal ultrasound-guided biopsy (TRUS-Bx) [1,2]. The designation of biopsy sites during standard systematic biopsies (TRUS-Bx) is random and operator dependent, and hence liable to sampling error. This results in a high rate of false negative results (up to 49% [3]), failure of detection of clinically significant PCa (csPCa), inaccurate tumour risk stratification, and detection of low-risk clinically insignificant cancer [4].

In the past years, the introduction of multiparametric magnetic resonance imaging (mpMRI) of the prostate in the diagnostic pathway of PCa significantly changed the diagnostic approach to this disease. Its high diagnostic accuracy for csPCa [5,6] has led to the inclusion of mpMRI into targeted biopsy strategies (MRI-TBx) in combination with the historically used TRUS-Bx, partially overcoming the drawbacks of conventional biopsy such as false negative results and, in turn, misdiagnosis of aggressive disease. Indeed, evidence suggests that MRI-TBx alone would miss up to 9–15% of csPCa [7–9], and the combination of MRI-TBx and TRUS-Bx provides the highest detection rate of csPCa [7,8,10]. However, this strategy is associated with an increased number of biopsy cores and frequently with increased detection of indolent disease [7,8,10]. This raises the question regarding whether, in current clinical practice, some patients might benefit from MRI-TBx alone to avoid the detection of insignificant PCa due to eventual systematic random sampling of the surrounding tissue. The rationale for this assumption is supported by the most recent meta-analyses showing that the MRI-TBx-alone approach could significantly reduce insignificant PCa detection rate [7,8]. We are still far from safely considering patients candidates for one biopsy strategy rather than another (ie, MRI-TBx alone or MRI-TBx + TRUS-Bx). In the current study, we hypothesised that upfront risk stratification with clinical and MRI parameters might help better stratify patients and identify those who have a low probability to harbour csPCa outside the index lesion (IL), and therefore they might undergo the MRI-TBx-alone approach. Relying on a large cohort of patients who underwent fusion targeted biopsy at a single European centre, we identified the predictors of csPCa outside the IL, in order to attempt to develop an individualised risk model to safely spare TRUS-Bx and select patients who can be submitted to MRI-TBx only. The validity of these findings was also tested in a large North American population.

## 2. Patients and methods

### 2.1. Study population

Between January 2013 and November 2017, 480 consecutive patients underwent mpMRI of the prostate with subsequent transrectal targeted fusion and concomitant systematic biopsy (TRUS-Bx) at a single European tertiary care referral centre (San Raffaele Hospital, Milan, Italy). All clinical and pathological data were prospectively collected from the first case performed within a review board-approved database. For the purpose of the present study, we excluded those patients with previous positive biopsy ($n$ = 63), as well as with positive DRE ($n$ = 61). Further exclusion criteria consisted of unknown PSA value ($n$ = 6) and prostate volume ($n$ = 11).

These selection criteria resulted in a final population of 339 assessable biopsy-naïve or previous negative biopsy patients.

A second cohort consisted of 441 biopsy-naïve or previous negative biopsy patients with a negative DRE who underwent mpMRI of the prostate with subsequent transrectal targeted fusion and concomitant TRUS-Bx at Mayo Clinic Hospital (Rochester, MN, USA) within the same time frame.

### 2.2. Multiparametric magnetic resonance imaging

All patients underwent a 1.5-T (Achieva and Achieva dStream; Philips Medical Systems, Best, The Netherlands) or 3-T mpMRI study (Discovery; GE Healthcare, Chicago, IL, USA) with phased array surface coil and endorectal coil (BPX-15; Bayer Medical Care, Indianola, PA, USA). According to the European Society of Urogenital Radiology guidelines [11], the imaging protocol consisted of multiplanar T2-weighted images, diffusion-weighted imaging (with $b$ values of 50–800–1600 s/mm$^2$ in the European cohort and 100–800–1600 s/mm$^2$ in the North American cohort; apparent diffusion coefficient maps were automatically elaborated), dynamic contrast-enhanced MRI, and delayed T1-weighted images with fat suppression.

In both centres for patients who had previously received one or more sets of biopsies, all mpMRI scans were performed at least after 4 wk from prostate biopsy, and precontrast T1-weighted images were performed to rule out postbiopsy haemorrhagic artefacts. The mpMRI images were scored and reported according to the Prostate Imaging Reporting and Data System (PI-RADS) version 1 (v.1) [11] and from 2015 on the subsequent PI-RADS version 2 (v.2) [12]. All PI-RADS v.1 images were retrospectively reviewed and assigned a PI-RADS v.2 category. Experienced radiologists analysed the mpMRI findings.

### 2.3. Prostate biopsy technique and histopathological examination

Software registration fusion approach was used to perform biopsy of the lesions visualised on mpMRI (targeted biopsy). Each patient was also concomitantly submitted to TRUS-Bx during the same session, in concordance with the currently available guidelines [1,13]. Random sampling was performed avoiding IL indicated as suspicious by mpMRI, keeping a margin distance of 5 mm. TRUS was performed using a Flex Focus 500 machine with a biplanar transducer (BK Medical, Herlev, Denmark) in both centres. Fusion biopsies were carried out by five experienced urologists (three in the European cohort and two in the North American cohort) using a 18-gauge needle and a biopsy gun providing a specimen size of 18–22 mm. Regarding the software registration fusion technique, before biopsy both the prostate and the region of interest were contoured and superimposed with the TRUS image, using the BioJet fusion system (D&K Technologies, Barum, Germany) in the European cohort [14] and the UroNav fusion system (Invivo Corp., Gainesville, FL, USA) in the North American cohort [15]. The technical data and usage of BioJet and UroNav fusion system have previously been described [15,16]. All prostate biopsy specimens were analysed by a dedicated uropathologist. To decrease the risk of sampling error caused by bleeding, oedema, and movement of artefacts, MRI-TBx was performed before random sampling.

### 2.4. Variable definition

All patients had complete clinical data consisting of age at biopsy, PSA values (ng/ml), prostate volume defined at mpMRI (ml), DRE (negative), PI-RADS (3 vs 4 vs 5), number of MRI lesions, number of targeted cores, number of random cores, and previous biopsy history (none vs previous negative biopsy). Primary and secondary Gleason grades were available separately for all cores taken at MRI-TBx and TRUS-Bx. If more than one lesion was present at mpMRI, the IL was defined as the highest PI-RADS assessment category or as the largest lesion in case of more than one within the same category.

### 2.5. Outcomes

The outcome of our study was to identify the independent predictors of csPCa outside the mpMRI-detected IL, in order to attempt to develop an individualised risk calculator to identify patients who might avoid systematic sampling of the prostate, due to their low probability to harbour csPCa, in addition to the targeted one. Clinically significant PCa outside the IL was defined as the presence of PCa with Gleason score $\geq$3 + 4 (International Society for Urological Pathology [ISUP] grade 2 or more) at TRUS-Bx.

### 2.6. Statistical analyses

The European cohort of 339 patients was used to develop a prebiopsy risk calculator for the prediction of presence of csPCa outside the IL. Age at biopsy, PSA value, prostate volume, PI-RADS (3 vs 4 vs 5), number of MRI lesions, and previous biopsy history (none vs negative) were used as predictors in multivariable logistic regression analysis assessing the outcome of interest. The predictive accuracy of the model was tested using the receiver operating characteristic-derived area under the curve (AUC). Furthermore, the extent of over- or underestimation of predicted probabilities relative to observed probabilities of csPCa outside the IL was assessed relying on a calibration plot. The multivariable-derived coefficients of the predictive model were used to calculate the risk of csPCa for each patient, and to construct the corresponding risk calculator to simplify individual risk estimation [17]. The performance characteristics of different risk-calculator thresholds were tested to quantify the number of avoidable biopsies versus the number of potentially missed csPCa. For each risk-calculator cut-off, sensitivity and negative predictive value (NPV) were also calculated. In order to evaluate the clinical impact of the new model, we relied on decision curve analysis as described by the model proposed by Vickers and Elkin [18], to evaluate and compare the net benefit. Finally, the same analyses were repeated in a different dataset, namely, a North American cohort ($n$ = 441), to assess whether similar findings were obtained.

All statistical tests were performed using the RStudio graphical interface v.0.98 for R software environment v.3.0.2 (R Foundation, Vienna, Austria). All tests were two sided, with a significance level set at $p < 0.05$.

## 3. Results

Table 1 summarises the descriptive characteristics of the European cohort. Overall, 215 men (63%) were biopsy naïve, while 124 (37%) underwent at least one previous negative biopsy. Overall, PCa and csPCa detection rates were 66% ($n$ = 224) and 55% ($n$ = 185), respectively. The csPCa detection rates for MRI-TBx and TRUS-Bx were 49% ($n$ = 165) and 41% ($n$ = 138). Of those patients identified with csPCa outside the IL, 103 (75%) had a Gleason score of 7 (ISUP grade 2–3), 22 (16%) had a Gleason score of 8 (ISUP grade 4), and 13 (9%) had a Gleason score of 9 (ISUP grade 5). The rates of csPCa missed by MRI-TBx and TRUS-Bx were 12% ($n$ = 22) and 26% ($n$ = 49), respectively.

**Table 1 – Descriptive characteristics of 339 patients who underwent mpMRI of the prostate and subsequent targeted and concomitant systematic biopsy at a single tertiary care European referral centre between 2013 and 2017**

| Variables | Overall ($n$ = 339) |
|---|---|
| Age at biopsy (yr) | |
| Median | 65 |
| IQR | 59–71 |
| PSA value (ng/ml) | |
| Median | 6.4 |
| IQR | 4.6–9.6 |
| Prostate volume (ml) | |
| Median | 48 |
| IQR | 37–65 |
| PI-RADS score, $n$ (%) | |
| 3 | 134 (40) |
| 4 | 147 (43) |
| 5 | 58 (17) |
| MRI lesions | |
| Median | 1 |
| IQR | 1–1 |
| Targeted cores | |
| Median | 3 |
| IQR | 2–3 |
| Random cores | |
| Median | 12 |
| IQR | 8–12 |
| Previous biopsy, $n$ (%) | |
| Biopsy naïve | 215 (63) |
| Previous negative biopsy | 124 (37) |
| Overall detection of PCa, $n$ (%) | 224 (66) |
| Overall detection of csPCa, $n$ (%) | 185 (55) |
| csPCa detection in targeted cores, $n$ (%) | 165 (49) |
| csPCa detection in random cores, $n$ (%) | 138 (41) |

csPCa = clinically significant PCa; IQR = interquartile range; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen.

At multivariable logistic regression analysis (Table 2), prostate volume (odds ratio [OR]: 0.98; 95% confidence interval [CI]: 0.97–0.99; $p$ = 0.001), PI-RADS 4 (OR: 3.77; 95% CI: 2.15–6.77; $p < 0.001$), PI-RADS 5 (OR: 9.48; 95% CI: 4.43–21.2; $p < 0.001$), and previous negative biopsy (OR: 0.43; 95% CI: 0.25–0.74; $p$ = 0.002) were independently associated with csPCa outside the IL. These independent predictors were used to construct a risk calculator to allow the estimate of the individual risk of csPCa outside the IL (Supplementary material).

The predictive accuracy of our model was 0.78, and the calibration was excellent (Fig. 1). Table 3 further illustrates the performance characteristics of different risk-calculator thresholds in the European cohort. The number of avoided systematic prostate biopsies, csPCa missed, sensitivity, and NPV are depicted for each threshold. The use of a cut-off of 15% would allow sparing of 16% (55/339) of TRUS-Bx at the cost of missing 7% (4/55) of csPCa outside the IL. The sensitivity and NPV associated with this cut-off were, respectively, 97% and 93%.

When compared with the select-all and select-none strategies at decision curve analysis (Fig. 2), the use of our

**Table 2 – Multivariable logistic regression model predicting csPCa outside the index lesion in 339 patients who underwent mpMRI of the prostate and subsequent targeted and concomitant systematic biopsy at a single tertiary care European referral centre between 2013 and 2017**

| Predictors | Multivariable analysis | |
|---|---|---|
| | OR (95% CI) | *p* value |
| Age | 1.03 (1.00–1.07) | 0.06 |
| PSA | 1.04 (1.00–1.09) | 0.05 |
| Prostate volume | 0.98 (0.97–0.99) | 0.001 |
| PI-RADS | | |
| 3 | Ref. | – |
| 4 | 3.77 (2.15–6.77) | <0.001 |
| 5 | 9.48 (4.43–21.2) | <0.001 |
| Number of MRI lesions | 1.07 (0.63–1.80) | 0.8 |
| Previous biopsy | | |
| Biopsy naive | Ref. | – |
| Previous negative | 0.43 (0.25–0.74) | 0.002 |

csPCa = clinically significant prostate cancer; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; Ref. = reference.

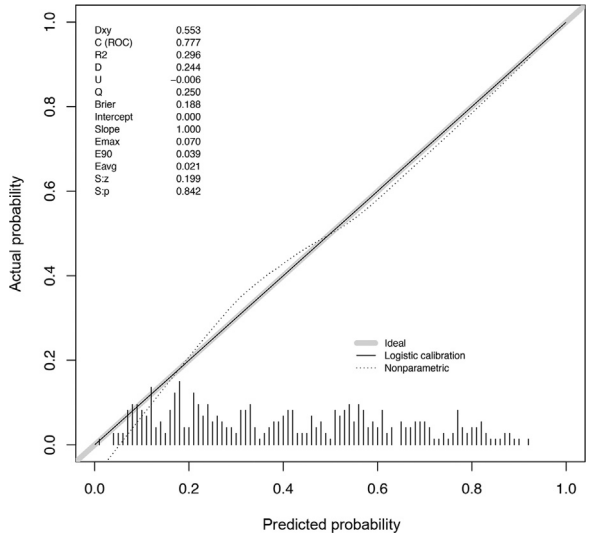


**Fig. 1 – Calibration plot of the risk calculator predicting csPCa outside the index lesion among 339 patients who underwent mpMRI of the prostate and subsequent targeted and concomitant systematic biopsy at a single European tertiary care referral centre between 2013 and 2017. The 45° line represents the ideal predictions. The *x* axis indicates the predicted probability of csPCa outside the IL, and the *y* axis indicates the observed rate of csPCa outside the IL. The dotted line represents the calibration of the multivariable model showing a good overlap between predicted and observed probabilities. csPCa = clinically significant prostate cancer; IL = index lesion; mpMRI = multiparametric magnetic resonance imaging.**

model resulted into a higher net benefit for high threshold probabilities, relative to performing TRUS-Bx in addition to MRI-TBx indiscriminately in all patients. Conversely, the net benefit was almost absent for threshold probabilities between 0% and 15%.

When we relied on the North American cohort (Supplementary Table 1), similar findings were observed. Specifically, at multivariable logistic regression analysis (Supplementary Table 2), age at biopsy (OR: 1.03; 95% CI: 1.01–1.06; $p = 0.02$), prostate volume (OR: 0.98; 95% CI: 0.97–0.99; $p < 0.001$), PI-RADS 4 (OR: 4.57; 95% CI: 2.58–8.38; $p < 0.001$), PI-RADS 5 (OR: 3.50; 95% CI: 1.80–6.98; $p < .001$), and previous negative biopsy (OR: 0.55; 95% CI: 0.34–0.90; $p = 0.02$) were independently associated with csPCa outside the IL. These independent predictors were used to develop a risk calculator to estimate the individual risk of csPCa outside the IL (Supplementary material).

The predictive accuracy of the North American model was 0.76 and the calibration was good (Supplementary Fig. 1). The use of a cut-off of 15% would allow sparing of 27% (119/441) of TRUS-Bx at the cost of missing 9% (11/119) of csPCa. The sensitivity and NPV associated with this cut-off were, respectively, 92% and 92% (Supplementary Table 3). When compared with the select-all and select-none strategies at decision curve analysis in the North American cohort, slight net benefit was observed for low-threshold probabilities (0–15%) of our model relative to performing TRUS-Bx in addition to MRI-TBx indiscriminately in all patients (Supplementary Fig. 2).

## 4. Discussion

Recent level 1 evidence observed that assessment of diagnostic pathway based on the performance of MRI before prostate biopsy and subsequent MRI-TBx alone, in the presence of a lesion suggestive of cancer, was superior to TRUS-Bx in all biopsy-naïve patients [19]. These findings raised a question regarding whether, in the presence of positive mpMRI, systematic sampling of the prostate should still be performed in addition to the targeted one. In fact, MRI-TBx alone can miss 9–15% of csPCa [7–9] mainly due to either technical targeting mistakes [20] or mpMRI limitations in detecting multifocal csPCa [21–24]. For this reason, general consensus has been developed to always perform TRUS-Bx in addition to MRI-TBx [1,9,13], at least until future risk tools are developed to help physicians safely identify which patients might benefit from a targeted sampling-alone approach [25].

In the current study, we postulated that *some* patients who are candidates for prostate biopsy have a low probability of harbouring csPCa outside the IL and therefore might benefit from an MRI-TBx-alone strategy. We assessed the independent predictors of csPCa outside the IL in two different cohorts aiming to develop a contemporary risk calculator that allows us to safely perform MRI-TBx alone omitting systematic sampling. Our findings failed to confirm our hypothesis.

First, in the European cohort, we identified clinical predictors of csPCa outside the IL, which formed the basis of our risk prediction model. Despite this novel risk calculator being accurate (AUC 0.78) and showing good calibration, using a cut-off of 15%, only 16% of patients would be spared prostate biopsies at the cost of missing 7% (4/55) of csPCa outside the IL (Table 3). The sensitivity (97%) and NPV (93%) associated with this cut-off are noteworthy; however, from a clinical point of view, the number of systematic biopsies spared compared with the number of aggressive PCa missed

**Table 3 – Performance characteristics of the risk calculator thresholds in the European cohort ($n$ = 339)**

| Risk (%) | Systematic biopsies | | csPCa | | Sensitivity (%) | NPV (%) |
|---|---|---|---|---|---|---|
| | Performed, $n$ (%) | Avoided, $n$ (%) | Found, $n$ (%) | Missed[a], $n$ (%) | | |
| ≥9 | 319 (94) | 20 (6) | 138 (43) | 0 (0) | 100 | 100 |
| ≥11 | 306 (90) | 33 (10) | 136 (44) | 2 (6) | 99 | 94 |
| ≥13 | 291 (86) | 48 (14) | 135 (46) | 3 (6) | 98 | 94 |
| ≥15 | 284 (84) | 55 (16) | 134 (47) | 4 (7) | 97 | 93 |
| ≥17 | 276 (81) | 63 (19) | 134 (49) | 5 (8) | 96 | 92 |
| ≥19 | 256 (76) | 83 (24) | 129 (50) | 9 (11) | 93 | 89 |
| ≥21 | 250 (74) | 89 (26) | 129 (52) | 9 (10) | 93 | 89 |
| ≥23 | 234 (69) | 105 (31) | 126 (54) | 12 (11) | 91 | 88 |
| ≥25 | 222 (66) | 117 (34) | 122 (55) | 16 (14) | 88 | 86 |

csPCa = clinically significant prostate cancer; NPV = negative predictive value.
[a] Patients below cut-off with csPCa.

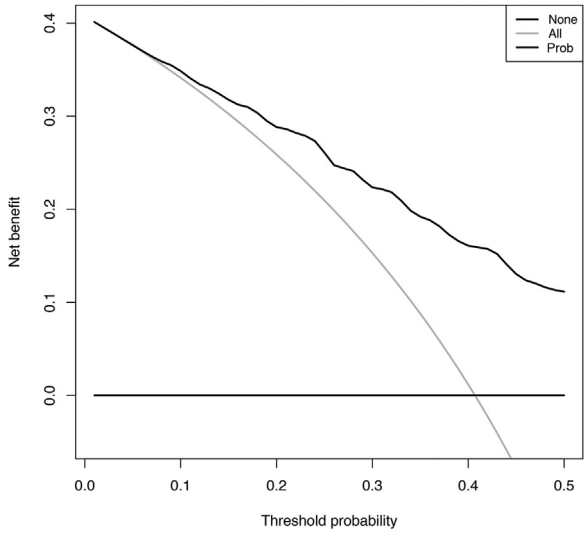


**Fig. 2 – Decision curve analysis in the European cohort.**

is negligible. This assumption is supported by the findings observed when we compared our novel model with the select-all and select-none strategies at decision curve analysis. Indeed, we failed to observe a net benefit for low-threshold probabilities (<15%) of our risk calculator relative to the common-use approach, namely, TRUS-Bx in addition to MRI-TBx, to all patients candidates for prostate biopsy (Fig. 2).

Second, to assess whether these findings were confirmed in a different cohort, we attempted to develop an individualised risk model to safely spare systematic sampling of the prostate in addition to targeted one in a North American population. The risk calculator that was developed performed well. Specifically, the AUC was 0.76 and the calibration was good. Upfront risk stratification with this risk model allows one to spare a higher number of systematic samples of the prostate than the European cohort (27% vs 16%). However, the rate of csPCa missed is noteworthy (9%). Again, we failed to observe a clinical benefit of the risk calculator developed in the North American cohort for low-threshold probabilities (<15%) relative to the standard of care (Supplementary Fig. 2).

To our knowledge, this study is the first to attempt to identify patients for whom an MRI-TBx-alone approach relative to TRUS-Bx + MRI-TBx could be considered. We observed that, regardless of the dataset used, even in men with a low probability to harbour significant disease around the IL, no useful clinical model can be developed to safely identify those patients who could avoid TRUS-Bx in addition to MRI-TBx. Therefore, to date, a combination of the two strategies represents the best option to adopt in daily clinical practice, during patient counselling and risk stratification.

Our findings should be interpreted in the light of recent evidence that suggested MRI-TBx alone as a possible approach in patients candidates for prostate biopsies. For example, Kasivisvanathan et al. [19] in the PRECISION trial compared the diagnostic efficacy of MRI-TBx alone with the standard of care, namely, TRUS-Bx. The authors observed that MRI-TBx alone detected a higher rate of csPCa (38% vs 26%; $p = 0.005$) and lower indolent disease (9% vs 22%; $p < 0.001$) [19]. Nonetheless, no results were provided regarding the number of csPCa missed by MRI-TBx alone, suggesting that this new approach might be risked in the absence of evidence to safely support its use. Arsov et al. [26] randomised 267 men to either MRI-TBx (arm 1) or the combination of MRI-TBx and TRUS-Bx (arm 2). No differences in terms of csPCa were observed between the study arms (29% vs 32%; $p = 0.7$). Moreover, even within arm 2, no additional value of TRUS-Bx to MRI-TBx was observed [26], suggesting that the omission of TRUS-Bx might be reasonable. However, if we carefully examine the findings of TRUS-Bx and MRI-TBx in arm 2 as separate tests, we can observe the following: (1) MRI-TBx and TRUS-Bx detected, respectively, 26% and 25% of csPCa; despite an absence of statistically significant difference, the combination of the two tests increased the detection of csPCa from 25–26% to 32%; and (2) MRI-TBx and TRUS-Bx missed, respectively, 18% and 21% of csPCa if only one of the two approaches was used [26]. Therefore, the combination of MRI-TBx and TRUS-Bx reduces the risk of misdiagnosis of csPCa relative to targeted sample alone, as supported by almost all the series [7,8,10]. In consequence, considering our findings and the aforementioned considerations, to date, it seems premature to support the extensive use of the MRI-TBx-alone approach

in patients candidates for prostate biopsy. This is particularly true for nonacademic centres where radiologists and urologists are still in the initial phase of their learning curve [27,28].

Our findings also deserve attention in consideration of the recent findings of MRI-FIRST trial; in this prospective, multicentre, paired diagnostic study, Rouviere et al. [29] provided evidence that the detection of csPCa is improved when both systematic and targeted biopsy are combined in biopsy-naïve patients. The authors observed that there was no significant difference in the detection of csPCa when TRUS-Bx and MRI-TBx were performed alone (30% and 32%, respectively; $p = 0.38$). However, both techniques had substantial added value in detecting ISUP grade group 2 or higher-grade tumours if used in combination (5.2% and 7.6%, respectively), since roughly one-third of csPCa were detected by only one biopsy technique.

Moreover, our results have important implications when looking at the preoperative risk assessment [25], especially in light of recent findings suggesting poor accuracy of mpMRI in detecting multifocal csPCa [21–24,30]. In this context, Borkowetz et al. [24], relying on radical prostatectomy (RP) specimens as reference standard, observed that mpMRI missed 16% of tumour foci, of which roughly 80% were aggressive tumours. In the same direction, Le et al. [22], in a study evaluating the ability of mpMRI in detecting PCa in RP specimens, observed that mpMRI missed 80% of nonindex tumours, even of high grade. Radtke et al. [23] reported that the combination of TRUS-Bx and MRI-TBx is associated with the highest detection rate of csPCa at final pathology. In the same direction, Stabile et al. [21] added value to this topic reporting for the first time that the poor accuracy of mpMRI in detecting multifocal aggressive disease is highly related to the PI-RADS score for the IL. Specifically, the authors observed that with the increase of PI-RADS score, the probability of harbouring csPCa outside the IL increased, suggesting that physicians should not quit performing a systematic sample of the prostate in addition to a targeted one [21]. Of fundamental importance is the observation that PCa with predominantly cribriform morphology, while associated with adverse outcome, is less visible on mpMRI than on other morphological patterns and thus is less likely to be detected on targeted biopsy [31,32]. In this context, although overall sensitivity of biopsy remains poor, combined approach with TRUS-Bx and MRI-TBx seems to yield the highest detection rates for cribriform PCa on final histopathology (TRUS-Bx: 21%; MRI-TBx: 29%; TRUS-Bx + MRI-TBx: 37%) [32].

In conclusion, our findings reinforce the general consensus that MRI-TBx should be performed in combination with TRUS-Bx [1,9,13] to reduce the misdiagnosis of aggressive disease, and to provide highest detection of multifocal aggressive PCa and, in turn, the most reliable pretherapeutic risk assessment [25].

Our study has several limitations. First, the use of TRUS-Bx as a reference test might have affected the reliability of our results due to the low NPV of this technique. Therefore, future studies that rely on more accurate reference tests (eg, 5-mm template biopsy [6], RP specimens) are needed to confirm our findings. However, given their more accurate nature, it is reasonable to expect a confirmation of our results.

Second, our findings must be interpreted with all the limitations applicable to retrospective studies. This implies several drawbacks. For example, the lack of standardisation in the number of targeted and random cores performed during prostate biopsy as well as in the type of magnetic field strength used (1.5 vs 3 T) might have introduced a bias. However, the real superiority of 3 T relative to 1.5 T is still under debate. Recent findings suggested comparable accuracy in terms of PI-RADS scoring and cancer location for 1.5 versus 3-T [33,34].

Third, the outcome of our study was csPCa defined as Gleason score $\geq 3 + 4$ ($\geq$ISUP grade 2), and our models were developed within a European and a North American cohort where the median number of systematic biopsy cores performed was 12. Therefore, our findings should be confirmed in a more extended systematic biopsy setting, using other definitions of csPCa.

## 5. Conclusions

To date, we are still far from safely identifying patients who might benefit from MRI-TBx alone, relying on the combination of patient characteristics and mpMRI parameters. Therefore, the combination of MRI-TBx and TRUS-Bx should strongly be considered the best available approach to reduce the risk of csPCa misdiagnosis and to provide the most reliable depiction of PCa multifocality.

***Author contributions***: Paolo Dell'Oglio had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Dell'Oglio, Stabile, Briganti.
*Acquisition of data:* Dell'Oglio, Stabile, Soligo.
*Analysis and interpretation of data:* Dell'Oglio, Stabile.
*Drafting of the manuscript:* Dell'Oglio, Stabile.
*Critical revision of the manuscript for important intellectual content:* Dell'Oglio, Stabile, Soligo, Brembilla, Esposito, Gandaglia, Fossati, Bravi, Dehò, De Cobelli, Montorsi, Karnes, Briganti.
*Statistical analysis:* Dell'Oglio, Stabile.
*Obtaining funding:* None.
*Administrative, technical, or material support:* None.
*Supervision:* Montorsi, Karnes, Briganti.
*Other:* None.

***Financial disclosures:*** Paolo Dell'Oglio certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor:*** None.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euo.2019.03.002.

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